

AMENDMENTS TO THE CLAIMS

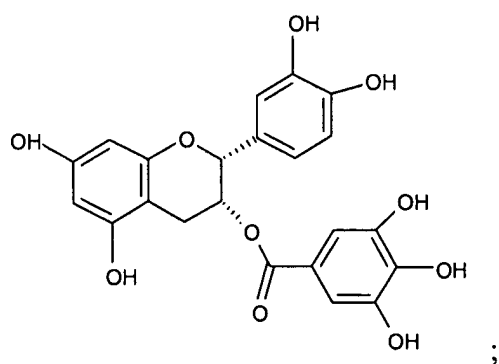
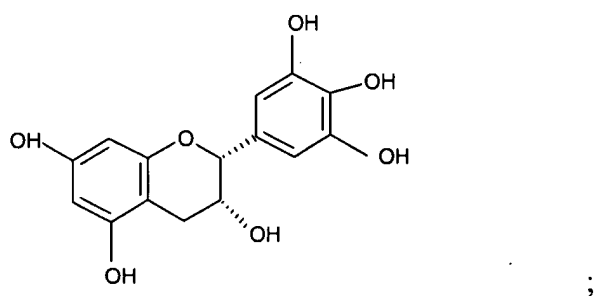
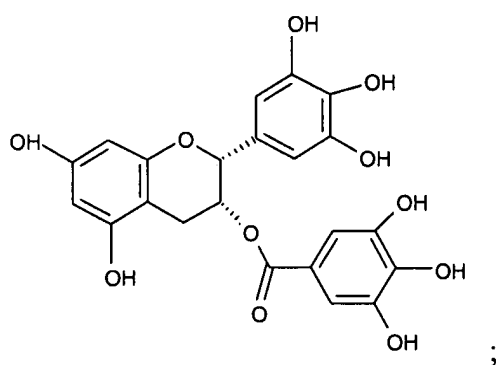
Kindly amend claims 16 and 30 and add new claim 33 as provided in the following claims listing.

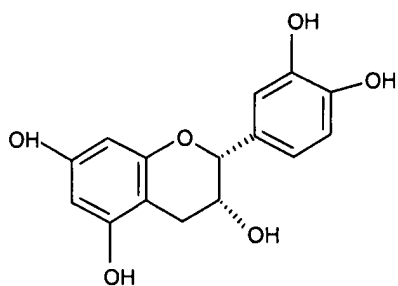
Claims Listing:

1. (Previously presented) A method for treating a patient with an actinic keratosis, the method comprising administering to said patient a composition comprising (i) a mixture of polyphenols and (ii) a carrier, wherein said composition comprises from $5 \pm 1\%$ (w/w) to $20 \pm 4\%$ (w/w) mixture of polyphenols, said mixture of polyphenols containing (-)-epicatechol, (-)-epicatechol gallate, (-)-epigallocatechol, (-)-epigallocatechol gallate, and (-)-gallocatechol gallate.
2. (Original) The method according to claim 1, wherein the patient is a human.
3. (Previously presented) The method according to claim 1, wherein at least one of the mixture of polyphenols is isolated from tea.
4. (Previously presented) The method according to claim 1, wherein at least one of the mixture of polyphenols is extracted from a tea.
5. (Previously presented) The method according to claim 4, wherein the tea is a green tea.
6. (Previously presented) The method according to claim 1, wherein at least one of the mixture of polyphenols is isolated from a tea extract.

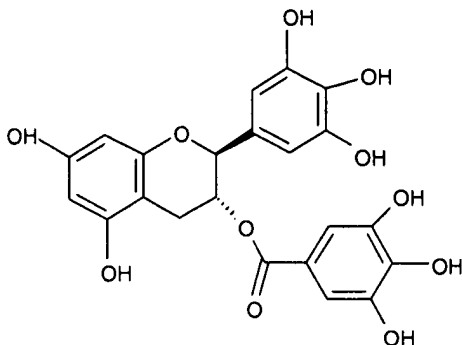
7. (Cancelled)

8. (Previously presented) The method according to claim 1, wherein the polyphenol has a formula selected from the group consisting of





; and



9-15. (Cancelled)

16. (Currently amended) The method according to claim 1, wherein the mixture of polyphenols contains about 2-20% (w/w) of (-)-epicatechol, about 2-20% (w/w) of (-)-epicatechol gallate, about 1-25% (w/w) of (-)-epigallocatechol, about 40-74% 40-75% (w/w) of (-)-epigallocatechol gallate and about 0.5-20% (w/w) of (-)-gallocatechol gallate.

17. (Cancelled)

18. (Previously presented) The method according to claim 1, wherein the mixture of polyphenols contains about 10.8% (w/w) of (-)-epicatechol, about 6.5% (w/w) of (-)-epicatechol gallate, about 9.2% (w/w) of (-)-epigallocatechol, about 54.8% (w/w) of (-)-epigallocatechol gallate and about 4.0% (w/w) of (-)-gallocatechol gallate.

19-22. (Cancelled).

23. (Previously presented) The method according to claim 1, wherein the composition comprises an additive selected from the group consisting of petroleum jelly, wax, oleyl alcohol, propylene glycol monostearate, propylene glycol monopalmitostearate and isopropyl myristate.

24. (Previously presented) The method according to claim 1, wherein the composition is administered topically.

25. (Previously presented) The method according to claim 1, wherein the composition is formulated as an emulsion, a gel, a cream, or an ointment.

26. (Original) The method according to claim 1, wherein the method for treating actinic keratosis is combined with a different anticancer treatment.

27. (Original) The method according to claim 26, wherein the different anticancer treatment is selected from the group consisting of surgery, electrodesiccation, curettage, excision, Mohs micrographic surgery, radiation, proton therapy, chemotherapy, photodynamic therapy, cryosurgery, laser, immunotherapy, vaccine therapy and biologic therapy.

28. (Withdrawn) The method according to claim 27, wherein the chemotherapy is carried out with an agent selected from the group consisting of podophyllin, 5-fluorouracil, bleomycin, interferon, imiquimod, and mixtures thereof.

29. (Withdrawn) The method according to claim 27, wherein the radiation is selected from the group consisting of X-ray radiation and γ -radiation.

30. (Currently amended) The method according to claim 1, wherein said composition comprises ~~from $10 \pm 1\%$ (w/w) to $20 \pm 2\%$~~ $10 \pm 2\%$ (w/w) mixture of polyphenols.

31. (Previously presented) The method according to claim 1, wherein said composition comprises $15 \pm 3\%$ (w/w) mixture of polyphenols.

32. (Previously presented) The method according to claim 31, wherein said mixture of polyphenols contains about 10.8% (w/w) of (-)-epicatechol, about 6.5% (w/w) of (-)-epicatechol gallate, about 9.2% (w/w) of (-)-epigallocatechol, about 54.8% (w/w) of (-)-epigallocatechol gallate and about 4.0% (w/w) of (-)-gallocatechol gallate.

33. (New) The method according to claim 1, wherein said composition comprises $20 \pm 2\%$ (w/w) mixture of polyphenols.

REMARKS

Claims 1-6, 8, 16, 18, 23-27, and 30-32 were pending and under examination in this case. Claims 28 and 29 were previously withdrawn. Claims 7, 9-15, 17, and 19-22 were previously cancelled. New claim 33 has been added with this reply. Thus, claims 1-6, 8, 16, 18, 23-27, and 30-33 are now pending and under examination in this case. Claims 16 and 30 stand rejected under 35 U.S.C. § 112, first paragraph, for lack of written description. Claims 1-6, 8, 16, 18, 23-27, and 30-32 stand rejected under 35 U.S.C. § 103 for obviousness. Each of these rejections is addressed separately below.

Support for Amendments to the Claims

Claims 16 has been amended to recite a range of “40-75% (w/w)” with respect to (-)-epigallocatechol gallate. Support for the range of various catechols recited in claim 16 is found in the specification at paragraph 49.

Claim 30 has been amended to recite “ $10 \pm 2\%$ (w/w) mixture of polyphenols.” Support for this range is found in the specification at paragraphs 12 and 13.

New claim 33 is directed to the use of a “ $20 \pm 2\%$ (w/w) mixture of polyphenols.” Support for this range is found in the specification at paragraphs 12 and 13.

No new matter has been added with these amendments.

Rejections under 35 U.S.C. § 112

Claims 16 and 30 stand rejected under 35 U.S.C. § 112, first paragraph, for lack of written description in the recited ranges.

As a basis for the rejection of claim 16, the Office finds that the term “40-74% (w/w) of (-)-epigallocatechol gallate” lacks written description. The Office notes that in view of the specification the upper end of this range should be 75%, and not 74%. Applicants have addressed this rejection by amendment of claim 16 to recite a range of “40-75% (w/w)” with respect to (-)-epigallocatechol gallate.

As a basis for the rejection of claim 30, the Office finds no support for the percentage range, “from $10 \pm 1\%$ (w/w) to $20 \pm 2\%$ (w/w) mixture of polyphenols,” recited in the claim. Applicants have addressed this rejection by amendment of claim 30 to recite a range of “ $10 \pm 2\%$ (w/w) mixture of polyphenols.”

In view of the amendments to the claims, Applicants respectfully request that the rejections for lack of written description be withdrawn.

Rejections under 35 U.S.C. § 103

Claims 1-6, 8, 16, 18, 23-27, and 30-32 stand rejected, under 35 U.S.C. § 103(a), as being unpatentable over Deckers or Bobier-Rival in combination with Miller et al. These rejections are respectfully traversed.

The pending claims are directed to methods for treating actinic keratosis by administering to a subject a composition containing from $5 \pm 1\%$ (w/w) to $20 \pm 4\%$ (w/w) mixed polyphenols. These polyphenols can be extracted from a variety of sources, including green tea leaves.

Deckers describes the use of emulsions in products for topical application to the skin (see Abstract) where one of numerous possible applications is the treatment of actinic keratosis (col. 25, lines 17-18). One possible ingredient of the emulsion is an anti-oxidant (col. 19, line 32) and among the anti-oxidants which can be used is listed green tea extract (col. 23, lines 1-12), along with twenty five other anti-oxidants. However, nowhere in Deckers is there any teaching that anti-oxidants should be included in a dermatological product for treating actinic keratosis. Nowhere in Deckers are there any specific examples of formulations that include green tea extract and nowhere is there any teaching of what amounts of green tea extract would be used. Furthermore, nowhere in Deckers is there a teaching or suggestion to use green tea extract for any purpose other than for use as an anti-oxidant. Thus, Deckers teaches nothing more than an amount of green tea extract consistent with its use as an anti-oxidant. Deckers fails to provide any

teaching or suggestion that green tea extracts are, by themselves, efficacious therapeutic agents and certainly fails to teach that they would be useful for the treatment of actinic keratosis.

Bobier-Rival describes the use of a cosmetic or dermatological composition containing a skin enhancing agent (see Abstract). One of the possible classes of skin enhancing agents is retinoids, which are known to be used in dermatology for treating actinic keratoses (see Abstract and col. 1, lines 33-34). However, retinoids are not related in any way to the polyphenols used in the Applicants' claimed methods. Most importantly, the only mention of tea extract in Bobier-Rival is in the formulation of Example 1 spanning columns 4 and 5. The formulation of Example 1 contains 0.20% (w/w) green tea extract, an amount consistent with the use of green tea extract as an antioxidant to preserve the formulation and at least **40 times lower** than the lowest value ($5 \pm 1\%$ (w/w) polyphenols) encompassed by the range recited in claim 1. Bobier-Rival fails to provide any teaching or suggestion that green tea extracts are, by themselves, useful for the treatment of actinic keratosis.

Miller teaches only that curettage may be used to treat actinic keratoses, never disclosing or suggesting the use of any polyphenol mixtures for actinic keratosis therapy.

In making this rejection the Office acknowledges the fact that the prior art of record fails to teach the claimed amounts of green tea polyphenols (Office Action at page 4).

As a basis for the rejection, the Office Action at page 6 states (emphasis added):

...green tea extracts have known antioxidant properties as noted by Deckers at col. 23, lines 1-15. Since antioxidants are well known to be highly desirable and beneficial when treating skin conditions and overall health in general, then it clearly would have been well within the purview of one of ordinary skill in the art to increase the amount of green tea polyphenols to the claimed amounts to achieve beneficial antioxidant properties from the green tea extract since the green tea extracts are known to have such beneficial antioxidant properties.

Thus, the Office asserts that the prior art of record can be modified to arrive at the claimed invention, the motivation to do so being found in the common knowledge that

antioxidants are useful for the treatment of skin conditions in general. Applicants respectfully disagree and address this rejection with the following remarks.

*Common Knowledge of the Benefits
of Antioxidants for the Treatment of
Skin Conditions in General is
Insufficient to Render the Treatment
of Actinic Keratosis Obvious*

Claim 1, and dependent claims 6, 8, 16, 18, 23-27, and 30-33, are directed to a method for treating a patient with an actinic keratosis using a concentrated, from $5 \pm 1\%$ (w/w) to $20 \pm 4\%$ (w/w), mixture of polyphenols. In rejecting these claims for obviousness the Office has found a motivation to modify the prior art of record based upon the common knowledge that antioxidants are useful in general for the treatment of skin conditions. Applicants respectfully disagree.

All words in a claim must be considered in judging the patentability of that claim against the prior art. MPEP 2143.03. The prior art can be modified or combined to reject claims as *prima facie* obvious as long as there is a reasonable expectation of success. MPEP 2143.02.

Accordingly, to establish a *prima facie* case for the obviousness of the pending claims the Office must identify a motivation to modify the prior art to arrive at the claimed method **for treating actinic keratosis**, not skin conditions in general.

None of the references relied upon by the Office in making this rejection teach or suggest that a green tea extract is, itself, beneficial for the treatment of actinic keratosis. Such a teaching or suggestion is required to establish a *prima facie* case for the obviousness of the pending claims.

Moreover, assuming, for the sake of argument, that one of skill in the art would be motivated, based upon the antioxidant properties of polyphenols alone, to apply green tea extracts to the skin of a subject suffering from actinic keratosis, Applicants note that the

Office fails to provide any motivation to modify the Deckers or Bobier-Rival to increase the amount of polyphenols in the prior art compositions. If, as asserted by the Office, Deckers and Bobier-Rival describe compositions containing polyphenols sufficient to produce the desired antioxidant effect, then there should be no motivation to increase the amount of polyphenols to arrive at the claimed invention just because the compositions are now being used to treat actinic keratosis.

Applicants submit that no *prima facie* case for obviousness has been established by the Office because the prior art relied upon by the Office in making this rejection fails to recognize that polyphenols and green tea extracts are therapeutically beneficial specifically for the treatment of actinic keratosis.

*Applicants Have Demonstrated
Unexpected Results*

Further, in maintaining the rejection for obviousness, the Office asserts, at page 8 of the Office Action, that the claims are not commensurate in scope with the unexpected results provided in Examples 1 and 2. Applicants respectfully disagree.

Applicants have demonstrated unexpectedly good results for the claimed invention. Indeed, it was entirely unanticipated that actinic keratoses would disappear completely following Applicants' claimed treatment. As demonstrated by the results presented in Examples 1 and 2 of the present application, in patients suffering from actinic keratoses for at least 10 years, treatment with Polyphenon E, an exemplary polyphenol mixture of the claims, resulted in resolution of **all keratoses** exhibited by the patients within **only 12-16 weeks**. This complete and rapid therapeutic effect was striking and would be considered by those of skill in this area to constitute an unexpectedly good result.

Consideration of rebuttal evidence and arguments requires Office personnel to weigh the proffered evidence and arguments. Office personnel should avoid giving

evidence no weight, except in rare circumstances. Furthermore, evidence of the unobviousness of a broad range can be proven by a narrower range when one skilled in the art could ascertain a trend that would allow him to reasonably extend the probative value thereof. MPEP 2145.

Applicants note that claims 18 and 32 are directed to methods for treating actinic keratosis using the specific mixture of polyphenols (10.8% (w/w) EC, 6.5% (w/w) ECG, 9.2% (w/w) EGC, 54.8% (w/w) EGCG, and 4.0% (w/w) GCG) that was used to treat human subjects and for which results are provided in Examples 1 and 2. Furthermore, claim 16 recites a narrow genus of polyphenol mixtures (2-20% (w/w) EC, 2-20% (w/w) ECG, 1-25% (w/w) EGC, 40-75% (w/w) EGCG, and 0.5-20% (w/w) GCG) encompassing Polyphenon E and which can also be useful for the treatment of actinic keratosis.

Even if the Office were to maintain that a *prima facie* case for obviousness has been established, Applicants assert that in view of the unexpected results provided in Examples 1 and 2, the subject matter of claims 16, 18, and 32 cannot be considered obvious, and the § 103 rejection for these claims should be withdrawn.

In view of the remarks above, Applicants respectfully request that the rejections for obviousness be withdrawn.

CONCLUSION

Applicants submit that this case is now in condition for allowance, and such action is respectfully requested.

Enclosed is a Petition to extend the period for replying to the Office action for 2 months, to and including March 23, 2009, and a check in payment of the required extension fee. Applicants note that March 21, 2009, was a Saturday.

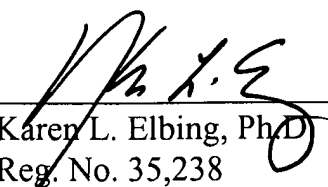
To expedite prosecution Applicants request a telephonic interview with the Examiner to discuss any remaining rejections. The Examiner is invited to call the

undersigned at 617-428-0200.

If there are any additional charges or any credits, please apply them to Deposit
Account No. 03-2095.

Respectfully submitted,

Date: 23 March 2009



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